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Authors
Liu, Danqian
Dan, Yang

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A Motor Theory of Sleep-Wake Control: Arousal-Action Circuit

Danqian Liu and Yang Dan

Department of Molecular and Cell Biology, Helen Wills Neuroscience Institute, and Howard Hughes Medical Institute, University of California, Berkeley, California 94720, USA; email: ydan@berkeley.edu

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sleep, arousal, circuit, autonomic nervous system, somatomotor system

Abstract

Wakefulness, rapid eye movement (REM) sleep, and non–rapid eye movement (NREM) sleep are characterized by distinct electroencephalogram (EEG), electromyogram (EMG), and autonomic profiles. The circuit mechanism coordinating these changes during sleep-wake transitions remains poorly understood. The past few years have witnessed rapid progress in the identification of REM and NREM sleep neurons, which constitute highly distributed networks spanning the forebrain, midbrain, and hindbrain. Here we propose an arousal-action circuit for sleep-wake control in which wakefulness is supported by separate arousal and action neurons, while REM and NREM sleep neurons are part of the central somatic and autonomic motor circuits. This model is well supported by the currently known sleep and wake neurons. It can also account for the EEG, EMG, and autonomic profiles of wake, REM, and NREM states and several key features of their transitions. The intimate association between the sleep and autonomic/somatic motor control circuits suggests that a primary function of sleep is to suppress motor activity.

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INTRODUCTION

Sleep is a behavioral state observed in all animals, even those without a centralized nervous system (Nath et al. 2017). In invertebrates and fish, sleep is identified by prolonged behavioral immobility together with an increased arousal threshold (Barlow & Rihel 2017, Hendricks et al. 2000, Raizen et al. 2008, Shaw et al. 2000) (**Figure 1*a***). For mammalian animal models, sleep is confirmed by electroencephalogram (EEG) recordings of brain activity in addition to electromyogram (EMG) measures of skeletal muscle activity (**Figure 1*b***). In human sleep studies, polysomnography typically includes measures of autonomic activity in addition to EEG and EMG (**Figure 1*c***). Indeed, sleep and wake states are associated with different cardiovascular, breathing, and body temperature profiles (Jones 2009).

Mammals, birds, and reptiles have distinct rapid eye movement (REM) and non–rapid eye movement (NREM) sleep (Aserinsky & Kleitman 1953, Shein-Idelson et al. 2016). Although both types of sleep are associated with behavioral immobility, they exhibit distinct EEG and autonomic activity patterns (de Zambotti et al. 2018, Jafari 2017, Jones 2009, Silvani & Dampney 2013). Unlike NREM sleep, which is characterized by synchronized EEG and reduced autonomic activity, REM sleep exhibits wake-like desynchronized EEG and complex autonomic profiles. The complete skeletal muscle paralysis measured by EMG allows for the unambiguous distinction of REM sleep from wakefulness.

To understand the brain mechanism controlling sleep and wakefulness, an important step is to identify the neurons promoting each state. More than half a century after the discovery of the ascending activating system (Moruzzi & Magoun 1949), we now know that multiple monoaminergic, cholinergic, and peptidergic systems promote wakefulness (Brown et al. 2012, Saper et al. 2010, Scammell et al. 2017) (**Figure 2*a***). However, the neural circuits promoting REM and NREM sleep are much less well understood. Over the past few years, rapid progress has been made to identify REM and NREM sleep neurons at the level of genetically defined cell types. It is now increasingly clear that sleep is controlled by large distributed networks spanning multiple brain regions, many of which are closely associated with somatomotor and autonomic regulation. Here we review the

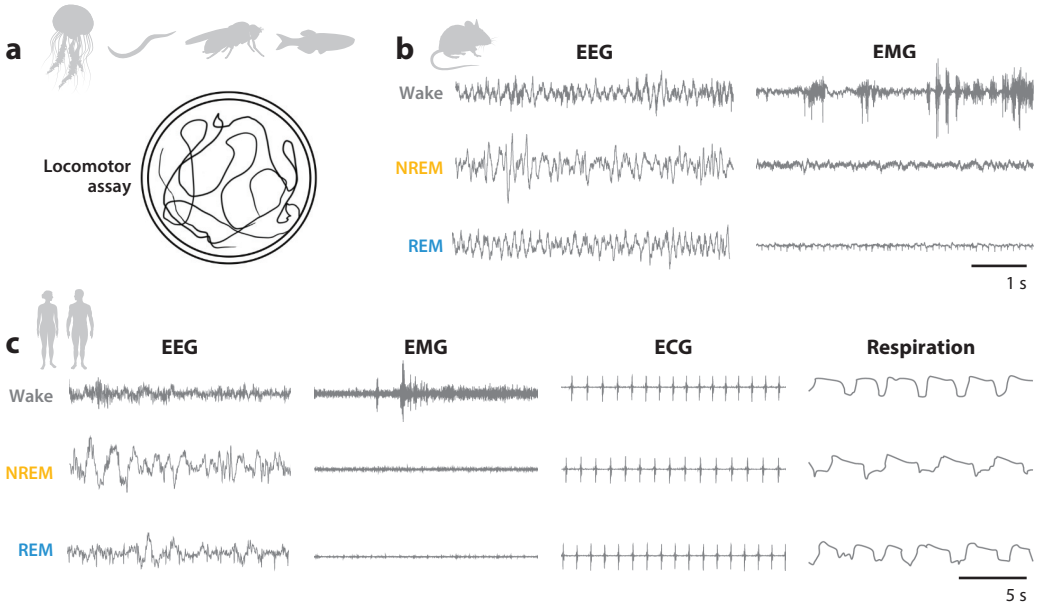


Figure 1

Sleep recordings in various animal models and humans. (*a*) In nonmammalian animals such as jellyfish, *Caenorhabditis elegans*, *Drosophila*, and zebrafish, locomotor assay is used to measure sleep. (*b*) Examples of mouse EEG and EMG recordings during wakefulness and NREM and REM sleep. (*c*) Example polysomnography recordings from a healthy human subject during wakefulness and NREM (stage 3) and phasic REM sleep. Several other recordings typically included in polysomnography (e.g., electrooculography) are not shown. Data for panel *c* from the ISRUC-SLEEP data set (Khalighi et al. 2016). Abbreviations: ECG, electrocardiography; EEG, electroencephalogram; EMG, electromyogram; NREM, non–rapid eye movement; REM, rapid eye movement.

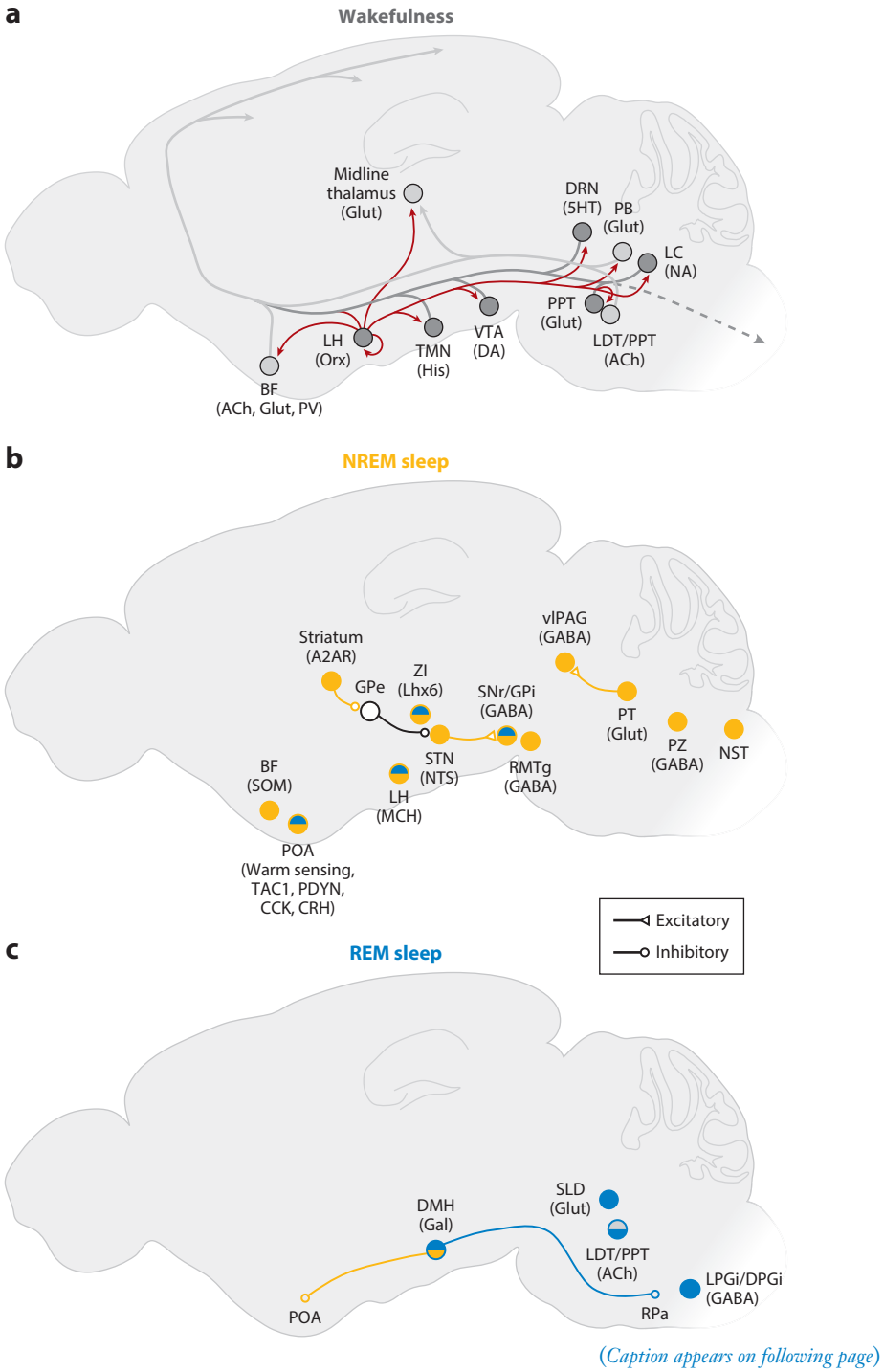
currently known REM and NREM sleep neurons, with a special focus on the recently identified populations. We then propose an arousal-action model in which the sleep control mechanism infiltrates the central autonomic and somatomotor control networks to coordinate the EEG, EMG, and autonomic changes associated with the global state of sleep.

CIRCUITS CONTROLLING NREM SLEEP

Hypothalamus

Following the seminal studies by Von Economo (1930) and Nauta (1946), the preoptic area (POA) of the hypothalamus has long been considered an important sleep center. Lesion and pharmacological inactivation of the POA can cause severe insomnia (Lin et al. 1989, Lu et al. 2000, McGinty & Sterman 1968, Sallanon et al. 1989), and c-Fos immunohistochemistry revealed sleep-active GABAergic neurons in the region (Gong et al. 2004, Sherin et al. 1996). However, both single-unit recordings and c-Fos immunohistochemistry indicate that the sleep-active neurons are spatially intermingled with wake-active neurons in the POA (Modirrousta et al. 2004, Szymusiak et al. 1998, Takahashi et al. 2009), making it difficult to target the sleep neurons specifically for circuit analysis.

A recent study used a c-Fos-based viral strategy to tag sleep-active neurons in the POA (Zhang et al. 2015). Subsequent chemogenetic activation of the tagged neurons induced a strong increase in NREM sleep, demonstrating their causal role in sleep generation. Using a similar strategy, the same research group showed that genetically tagged warm-sensing neurons in the medial and



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Summary of wakefulness-, NREM sleep–, and REM sleep–promoting neurons. (*a*) Wakefulness-promoting neurons with lines indicating their projections. The extensive projections of orexin neurons to other wakefulness-promoting neurons and among themselves (*red lines*), wakefulness/REM-active neurons (*light gray circles*), and wakefulness-active neurons (*dark gray circles*) are shown. Neuronal types include 5HT, ACh, DA, GABAergic PV, Glut, His, NA, and Orx. Brain regions include the BF, DRN, LC, LDT, LH, midline thalamus, PB, PPT, TMN, and VTA. (*b*) NREM sleep–promoting neurons (*yellow circles*) and neurons promoting both REM and NREM sleep (*yellow/blue circles*). Neuronal types include GABA; A2AR, CCK, CRH, GABAergic SOM, Glut, Lhx6, MCH, PDYN, and TAC1; and glutamatergic NTS. Brain regions include the BF, GPe, GPi, LH, NST, POA, PT, PZ, RMTg, SNr, STN, striatum, vlPAG, and ZI. (*c*) REM sleep–promoting neurons (*blue circles*). Neuronal types include the ACh, GABA, GABAergic Gal, and Glut, and brain regions include the DMH, DPGi, LDT, LPGi, POA, PPT, RPa, and SLD. Abbreviations: 5HT, serotonergic; A2AR, adenosine 2A receptor-expressing; ACh, cholinergic; BF, basal forebrain; CCK, cholecystokinin-expressing; CRH, corticotropin releasing hormone-expressing; DA, dopaminergic; DMH, dorsomedial hypothalamic nucleus; DPGi, dorsal paragigantocellular nucleus; DRN, dorsal raphe nucleus; GABA, GABAergic; Gal, galanin-expressing; Glut, glutamatergic; GPe, external globus pallidus; GPi, internal globus pallidus; His, histaminergic; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; Lhx6, LIM homeodomain factor-expressing; LPGi, lateral paragigantocellular nucleus; MCH, melanin-concentrating hormone-expressing; NA, noradrenergic; NREM, non–rapid eye movement; NST, nucleus of solitary tract; NTS, neurotensin-expressing; Orx; orexinergic; PB, parabrachial nucleus; PDYN, prodynorphin-expressing; POA, preoptic area; PPT, pedunculopontine nucleus; PT, pontine tegmentum; PV, parvalbumin-expressing; PZ, parafacial zone; REM, rapid eye movement; RMTg, rostromedial tegmental nucleus; RPa, raphe pallidus area SLD, sublateral dorsal nucleus; SNr, substantia nigra pars reticulata; SOM, somatostatin-expressing; STN, subthalamic nucleus; TAC1, tachykinin 1-expressing; TMN, tuberomammillary nucleus; vlPAG, ventrolateral periaqueductal gray; VTA, ventral tegmental area; ZI, zona incerta.

median POA also promote NREM sleep (Harding et al. 2018) (**Figure 2*b***). As sleep onset is known to be correlated with core body cooling and facilitated by skin warming (Krauchi et al. 1999, Morairty et al. 1993, Van Someren 2006), these POA neurons provide a mechanistic link between sleep and temperature regulation.

Based on the observation that sleep-active neurons labeled by c-Fos staining project strongly to the histaminergic tuberomammillary nucleus (TMN) (Sherin et al. 1998, Steininger et al. 2001), and that this projection plays an important role in sleep generation (Sallanon et al. 1989), the POA to TMN projection was used as an anatomical feature to single out POA sleep neurons (Chung et al. 2017). The TMN-projecting POA GABAergic neurons were tagged with a retrograde lentivirus (Cetin & Callaway 2014), and optrode recording and bidirectional optogenetic manipulations showed that these neurons are both sleep active and sleep promoting. Gene profiling revealed several neuropeptide markers selectively enriched in these neurons, including cholecystokinin (CCK), corticotropin releasing hormone (CRH), tachykinin 1 (TAC1), and prodynorphin (PDYN). Optogenetic and chemogenetic manipulations in corresponding Cre mice confirmed that the POA neurons labeled by each marker promote sleep (**Figure 2*b***). The basal forebrain, a region adjacent to the POA, is also involved in sleep-wake regulation (Buzsaki et al. 1988, McGinty & Sterman 1968), and it contains spatially intermingled sleep- and wake-active neurons (Hassani et al. 2009a, Szymusiak & McGinty 1989, Takahashi et al. 2009). Optogenetic activation of somatostatin (SOM)-expressing GABAergic neurons was found to promote NREM sleep, and a subset of SOM neurons are NREM sleep active (Xu et al. 2015). Given the diversity of Cre-dependent viral tools for activity manipulation, imaging, and circuit tracing (Deisseroth 2011, Oh et al. 2014, Osakada & Callaway 2013, Sternson & Roth 2014, Tian et al. 2012), the identification of sleep neurons at the level of genetically defined cell types can greatly facilitate future studies of the sleep control network. Furthermore, the various neuropeptides selectively enriched in the POA sleep neurons play important roles in autonomic regulation (Beaulieu & Lambert

1998). Their presence in sleep-promoting neurons could strengthen the coupling between sleep and autonomic regulation.

In addition to the POA, sleep neurons have been found in other regions of the hypothalamus. Optogenetic or chemogenetic activation of GABAergic neurons in the lateral hypothalamus expressing melanin-concentrating hormone (MCH) promotes both REM and NREM sleep (Jego et al. 2013, Konadhode et al. 2013, Tsunematsu et al. 2014) (**Figure 2*b***). A separate GABAergic population in the nearby zona incerta (ZI), which expresses the LIM homeodomain factor Lhx6, is activated by sleep pressure, and its chemogenetic activation promotes REM and NREM sleep (Liu et al. 2017). In the dorsomedial hypothalamic nucleus (DMH), the subset of galanin-expressing GABAergic neurons that projects to the POA is preferentially active during NREM sleep, and its optogenetic activation promotes NREM sleep while suppressing REM sleep (Chen et al. 2018).

Basal Ganglia

The basal ganglia, consisting of multiple structures in the forebrain and midbrain, has been studied extensively with regard to motor control (Gerfen & Surmeier 2011). Lesion experiments showed that several components of the basal ganglia are also involved in sleep-wake regulation (Gerashchenko et al. 2006, Lai et al. 1999, Qiu et al. 2010). In the nucleus accumbens, part of the ventral striatum critical for reinforcement and reward, activation of adenosine A2A receptor–expressing GABAergic neurons promotes NREM sleep (Oishi et al. 2017). A similar effect was shown for A2A receptor neurons in regions of the dorsal striatum (Yuan et al. 2017) (**Figure 2*b***). Notably, these striatal neurons are part of the basal ganglia indirect pathway, with well-studied functions in motor suppression (Gerfen & Surmeier 2011, Kravitz et al. 2010).

In the substantia nigra pars reticulata (SNr), bidirectional optogenetic and chemogenetic manipulations demonstrated the powerful role of GABAergic neurons in promoting both REM and NREM sleep (Liu et al. 2018) (**Figure 2*b***). Analysis of natural home cage behavior showed that mice transition sequentially through several behavioral states (locomotion, nonlocomotor movement, quiet wakefulness, and sleep), and activation/inactivation of SNr neurons promotes/suppresses sleep by biasing the direction of progression through the natural behavioral sequence. The sleep-promoting effect of SNr GABAergic neurons is likely mediated in part by their inhibition of multiple wake-promoting monoaminergic populations, including midbrain dopaminergic neurons. Both the direct chemogenetic inactivation of dopaminergic neurons in the ventral tegmental area (VTA) (Eban-Rothschild et al. 2016) and the inhibition of VTA neurons induced by activating GABAergic neurons in the rostromedial tegmental nucleus (Yang et al. 2018) were shown to increase sleep. Upstream of the SNr, a major source of glutamatergic input is the subthalamic nucleus (STN). Optogenetic activation of neurotensin-expressing glutamatergic neurons in the STN promotes NREM sleep as well. As the glutamatergic STN neurons and GABAergic SNr neurons are key parts of the indirect pathway (Gerfen & Surmeier 2011, Kravitz et al. 2010), they may play important roles in coordinating motor suppression and sleep generation, two tightly coupled behavioral processes (Campbell & Tobler 1984).

Periaqueductal Gray

The periaqueductal gray (PAG), a prominent midbrain structure, is known to coordinate somatic and autonomic responses to pain and threats (Behbehani 1995). It contains several functional columns, each of which extend longitudinally along the rostrocaudal axis. Activation of dorsal and lateral columns can elicit fight-or-flight responses, but activating the ventrolateral periaqueductal gray (vlPAG) evokes passive coping behaviors involving both somatic and autonomic changes

such as immobility, hypotension, and bradycardia (Bandler & Keay 1996, Carrive 1993, Tovote et al. 2016).

Previous lesion and pharmacological inactivation experiments showed that the vlPAG also plays a powerful role in gating REM sleep (Kaur et al. 2009, Lu et al. 2006b, Sastre et al. 1996, Vanini et al. 2007). Many GABAergic neurons in the vlPAG and the adjacent deep mesencephalic reticular nucleus (DpMe) express c-Fos in REM-deprived rats (Sapin et al. 2009), and a recent study using optrode recording confirmed that the majority of vlPAG GABAergic neurons are selectively suppressed during REM sleep (Weber et al. 2018). Pharmacogenetic activation of the DpMe GABAergic neurons or their glutamatergic input from the pontine tegmentum suppressed REM sleep while enhancing NREM sleep (Hayashi et al. 2015) (**Figure 2*b***). Optogenetic activation of vlPAG GABAergic neurons, on the other hand, strongly increased NREM sleep at the expense of both wakefulness and REM sleep (Weber et al. 2015, 2018). Rabies virus–mediated circuit tracing showed that, in addition to the putative REM sleep–promoting glutamatergic neurons in the dorsal pontine tegmentum, vlPAG GABAergic neurons also innervate wake-promoting serotonergic neurons in the dorsal raphe (DR) (Weissbourd et al. 2014) and noradrenergic neurons in the locus coeruleus (LC) (Weber et al. 2018). These observations suggest that a general function of the vlPAG neurons is to promote NREM sleep rather than specifically suppressing REM sleep.

NREM sleep is known to be associated with behavioral quiescence (Campbell & Tobler 1984) and reduced blood pressure and heart rate (de Zambotti et al. 2018, Jafari 2017, Silvani & Dampney 2013). These somatomotor and autonomic changes all occur in the same direction as those during passive emotional coping (Bandler & Keay 1996, Carrive 1993, Tovote et al. 2016). Thus, the vlPAG appears to be a point of convergence for the autonomic and somatomotor networks and participates in both passive emotional coping and NREM sleep generation.

Medullary NREM Zones

The parabrachial nucleus (PB) in the hindbrain, another node in the central autonomic network, plays important roles in signaling pain and threats and promoting arousal (Campos et al. 2018, Fuller et al. 2011, Han et al. 2015, Kaur et al. 2017). Retrograde tracing from the PB labeled many GABAergic neurons in the parafacial zone (PZ) in the medulla that express c-Fos after sleep (Anaclet et al. 2012). Chemogenetic activation of PZ GABAergic neurons causes a strong increase in NREM sleep while suppressing both wakefulness and REM sleep (Anaclet et al. 2014), whereas lesion of the PZ causes insomnia. A recent study showed that a subset of PZ neurons is NREM-active (Alam et al. 2018).

Early transection, electrical stimulation, and pharmacological inactivation experiments showed that neurons in the solitary tract nucleus, another key region of the central autonomic network, can also enhance sleep and reduce the EEG desynchronization evoked by stimulating the ascending reticular activating system (Batini et al. 1958, Magnes et al. 1960). Subsequent studies revealed the existence of NREM sleep–active neurons in this region (Eguchi & Satoh 1980). In future studies, it would be of great interest to clarify the relationship between the neurons involved in sleep generation versus autonomic regulation.

CIRCUITS CONTROLLING REM SLEEP

Pontine Tegmentum

Transection studies pioneered by Jouvet (1962) indicate that REM sleep generation depends critically on the hindbrain. In particular, numerous lesion and pharmacological experiments have indicated a key role of the pontine tegmentum (Amatruda et al. 1975, Boissard et al. 2002, George

et al. 1964, Gnadt & Pegram 1986, Kohyama et al. 1998, Lu et al. 2006b), which contains a mixture of cholinergic, noradrenergic, glutamatergic, and GABAergic neurons. Although cholinergic neurons in the pedunculopontine tegmentum (PPT) and laterodorsal tegmentum (LDT) have long been thought to be involved in REM sleep generation (Boucetta et al. 2014, Brown et al. 2012, Hobson et al. 1975, Van Dort et al. 2015), electrophysiological recording and c-Fos immunohistochemistry showed that many REM sleep–active cells are glutamatergic or GABAergic (Boucetta et al. 2014, Clement et al. 2011, Lu et al. 2006b, Maloney et al. 2000) (**Figure 2*c***). Genetic disruption of glutamatergic transmission causes the reduction and fragmentation of REM sleep (Krenzer et al. 2011), pointing to an important role of glutamatergic neurons in REM sleep generation. Cell-type-specific calcium imaging in freely moving mice revealed the existence of both wake- and REM sleep–active glutamatergic neurons, with the relative densities of these neurons varying along the mediolateral axis (Cox et al. 2016). An important challenge for future studies is to identify molecular markers or anatomical features that can be used to separate the REM sleep and wake neurons.

Medullary REM Zones

In addition to the pons, the lateral paragigantocellular nuclei (LPGi) and dorsal paragigantocellular nuclei in the medulla also contain c-Fos-labeled, REM sleep–active neurons (Sapin et al. 2009). As the LPGi projects to the spinal cord, it is believed to play an important role in REM sleep atonia (Magoun & Rhines 1946, Schenkel & Siegel 1989). A recent study showed that optogenetic activation of LPGi GABAergic neurons reliably triggered the NREM to REM sleep transition and prolonged REM sleep episode duration, and optrode recording showed that the neurons are REM sleep active. As the activity of these neurons causes not only muscle atonia but also the EEG activation characteristic of REM sleep, they constitute a core component of the REM generation network (**Figure 2*c***). Notably, activation of the LPGi inhibitory neurons was also shown to suppress locomotor activity (Capelli et al. 2017). Together with the dual role of SNr neurons in motor suppression and sleep generation (see above), these findings suggest a common theme of shared sleep and motor control neurons at multiple stages of the pathway.

In addition to the pons and medulla, recent studies have shown that multiple groups of neurons in the hypothalamus promote REM as well as NREM sleep. As summarized in **Figure 2*b***, these include MCH-expressing neurons in the lateral hypothalamus (Hassani et al. 2009b, Jego et al. 2013, Konadhode et al. 2013, Tsunematsu et al. 2014), Lhx6-expressing ZI neurons (Liu et al. 2017), and CCK- or CRH-expressing POA neurons (Chung et al. 2017). In the DMH, on the other hand, the galanin-expressing neurons projecting to the raphe pallidus are preferentially active during REM sleep, and their optogenetic activation promotes REM sleep at the expense of NREM sleep (Chen et al. 2018) (**Figure 2*c***).

AROUSAL-ACTION CIRCUIT FOR SLEEP-WAKE CONTROL

As summarized above, we now know that sleep neurons are widely distributed across multiple brain regions, spanning the forebrain, midbrain, and hindbrain (**Figure 2**). Thus, almost a century after the landmark study by Von Economo (Von Economo 1930), the notion of a single sleep center in the anterior hypothalamus seems to have been overturned. However, these findings also raise an important question: Are the newly discovered sleep neurons just a haphazard collection of cells that happen to promote sleep, or is there logic governing the organization of a highly distributed network? We believe that the known functions of these neurons, besides sleep regulation, provide an important clue.

First, sleep neurons have been found at multiple stages of the basal ganglia indirect pathway, including the dorsal and ventral striatum (Oishi et al. 2017, Yuan et al. 2017), STN, and SNr (Liu et al. 2018), all of which are involved in movement suppression (Gerfen & Surmeier 2011, Kravitz et al. 2010). At the brainstem level, inhibitory neurons in the LPGi suppress locomotor activity (Capelli et al. 2017) and promote REM sleep (Weber et al. 2015). Given that behavioral immobility is a defining feature of sleep in animals ranging from jellyfish to worms and flies to humans (Campbell & Tobler 1984, Hendricks et al. 2000, Nath et al. 2017, Raizen et al. 2008, Shaw et al. 2000), the existence of sleep neurons at multiple stages of the motor control pathway is unlikely to be coincidental. Second, several brain areas containing sleep neurons—such as the hypothalamus, vlPAG, and nucleus of the solitary tract—are closely involved in autonomic regulation (Llewellyn-Smith & Verberne 2011). It is well known that wake-sleep transitions are accompanied by marked changes in the heart rate, blood pressure, and body temperature (de Zambotti et al. 2018, Jafari 2017, Jones 2009, Silvani & Dampney 2013, Van Someren 2006), and the sleep neurons at key nodes of the central autonomic network may coordinate the regulation of both brain states and autonomic functions. In fact, besides brain activity measured by EEG, autonomic and somatomotor activities provide the most reliable readout of sleep and wake states. From a circuit design point of view, it seems to make perfect sense for the sleep control network to infiltrate both the autonomic and somatomotor circuits to coordinate the changes in the brain and the rest of the body to generate the global state of sleep.

Based on the simple observations above, we propose an arousal-action (AA) circuit for sleep-wake control. Its most distinct features are that (*a*) the wake-promoting neurons are separated into two categories, arousal and action neurons, with different brain state–dependent activity and connectivity with REM and NREM sleep neurons, and (*b*) the REM and NREM sleep neurons are part of the central somatic and autonomic motor circuits (**Figure 3**). Compared to previous models focusing on pairwise brain state transitions, such as the predator-prey model for the REM-NREM sleep transition (McCarley & Hobson 1975) and the flip-flop model for sleep-wake (Saper et al. 2001) or REM-NREM sleep transition (Lu et al. 2006b), the AA model is designed to explain all the transitions among wake and REM and NREM sleep states.

Basic Elements of the Arousal-Action Model

Below is a brief description of the basic elements of the model, consisting of neurons promoting each of the three brain states.

Wake-promoting neurons. Wake-promoting neurons consist of two categories referred to as the arousal and action neurons (**Figure 3*a***). Firing of the arousal neurons promotes EEG desynchronization, but it is insufficient to cause somatomotor/EMG activation. Action neurons, in contrast, cause direct autonomic and somatomotor activation and EEG desynchronization. These neuronal types are considered separately because EEG activation can be decoupled from autonomic and somatomotor activation, as observed during REM sleep.

Although the action neurons are only active during wakefulness, the arousal neurons are active during both wakefulness and REM sleep. The two types of neurons provide reciprocal excitation (**Figure 3*a***), which serves to coordinate EEG, autonomic, and somatomotor activation to meet the various behavioral demands during wakefulness. As a result, although the arousal neurons are wake/REM sleep active, experimental stimulation of these neurons promotes only wakefulness and not REM sleep, because of their excitation of the action neurons that leads to EMG activation. In addition, we propose recurrent excitation within the action neuron population, which enhances the stability of the wake state and its associated EMG activation. Biologically, this may

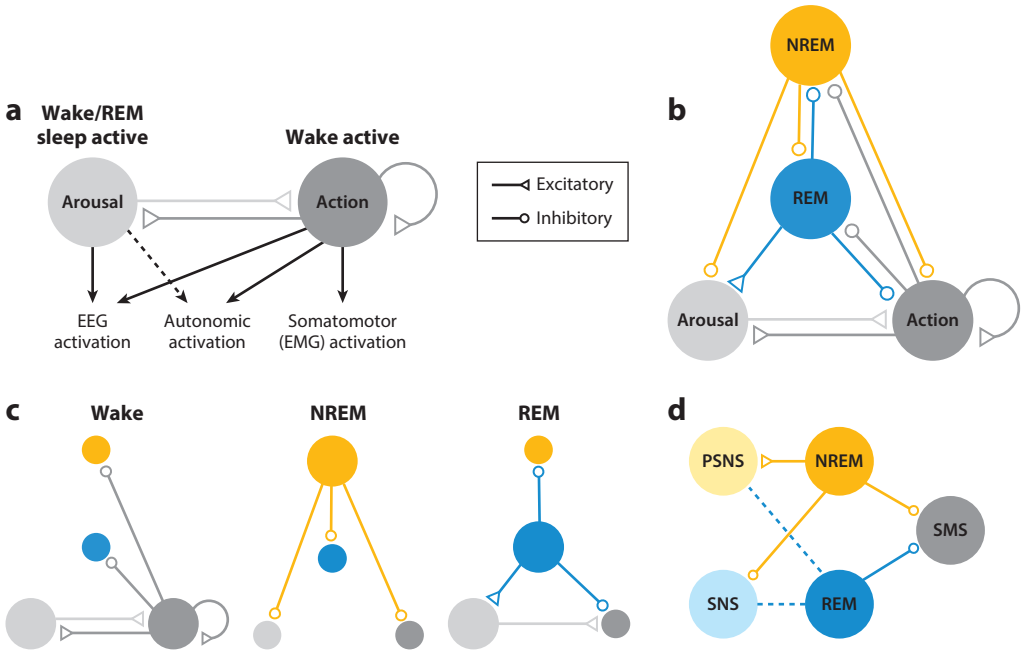


Figure 3

The AA circuit for sleep-wake control. (*a*) Arousal neurons (wake/REM sleep–active; *light gray*) that cause EEG activation. Action neurons (wake-active; *dark gray*) cause somatomotor, autonomic, and EEG activation. Lines indicate excitation connections between the two populations and within the action neuron population. (*b*) Excitatory and inhibitory interactions among wake and NREM and REM sleep neurons in the AA model. (*c*) Activity levels of different neuronal populations during each brain state (indicated by circle size). Only connections in which the presynaptic neurons are active during the corresponding brain state are indicated. (*d*) Predicted interactions between sleep neurons and SMS or autonomic nervous systems. The effect of REM neurons on the autonomic systems appears complex and is thus represented by dashed lines. Abbreviations: AA, arousal-action; EEG, electroencephalogram; EMG, electromyogram; NREM, non–rapid eye movement; PSNS, parasympathetic nervous system; REM, rapid eye movement; SMS, somatomotor; SNS, sympathetic nervous system.

involve orexin/hypocretin neurons (Li et al. 2002, Yamanaka et al. 2010), the loss of which causes weakening of the recurrent excitation and thus a destabilization of somatomotor activation, giving rise to narcolepsy and cataplexy (Broughton et al. 1986, Saper et al. 2010).

NREM sleep–promoting neurons. Neurons that promote NREM sleep (**Figure 3*b***) are NREM active, and they inhibit both arousal and action neurons, leading to reduced EEG, autonomic, and somatomotor activation. The NREM neurons may receive inhibitory inputs from both wake- and REM sleep–promoting neurons to ensure rapid and complete transitions between brain states, as proposed in the flip-flop circuit (Lu et al. 2006a, Saper et al. 2001). Although, for the sake of simplicity, we only indicate inhibition from action neurons in **Figure 3*b***, inhibition from arousal neurons should not be excluded.

REM sleep–promoting neurons. REM sleep–promoting neurons (**Figure 3*b***) are REM active. Although they inhibit action neurons to generate REM atonia, they may excite arousal neurons to cause EEG desynchronization. The REM neurons are likely to form reciprocal inhibition with both NREM and action neurons to ensure rapid brain state transitions (Lu et al. 2006b, Weber et al. 2015).

Note that in this simple conceptual model, each category of neurons contains multiple neuronal populations releasing diverse neurotransmitters and modulators (see the section titled Neuronal Instantiation of the Arousal-Action Model). The excitatory and inhibitory connections depicted in **Figure 3*b*** could be direct/monosynaptic or indirect/polysynaptic.

Wake, NREM, and REM State Transitions

The AA model can explain several key features of brain state transitions, as outlined below. The activity levels of the different neuronal categories during each brain state are summarized in **Figure 3*c***.

Lack of wakefulness → REM sleep transition. Direct transition from wakefulness to REM sleep is rarely observed in healthy subjects and is an important diagnostic marker for narcolepsy. According to the AA model, both arousal and action neurons are activated during wakefulness (**Figure 3*c***); the reciprocal excitation between them and among action neurons can effectively sustain the activity of both categories, stabilizing the wakeful state. Unlike NREM neurons, which simultaneously inhibit arousal and action neurons to trigger the wakefulness to NREM sleep transition, REM neurons inhibit action neurons but excite arousal neurons, which in turn excite action neurons. Thus, even if REM neurons are transiently activated during wakefulness, their inhibitory input to the action neurons cannot overcome the powerful excitation from both arousal and action neurons, thus failing to cause the wakefulness to REM sleep transition. On the other hand, weakening of the excitatory inputs to action neurons, especially the recurrent excitation among themselves (e.g., due to the loss of orexin/hypocretin signaling), makes it easier for the REM neurons to suppress the action neurons and trigger the wakefulness to REM sleep transition, as is observed in narcolepsy (Chemelli et al. 1999, Lin et al. 1999).

Presence of the NREM → REM sleep transition. During NREM sleep, both arousal and action neurons are inhibited by NREM neurons (**Figure 3*c***). When REM neurons are activated (e.g., due to accumulated REM sleep pressure), they can excite arousal neurons while maintaining the inactive state of action neurons. This is possible because, unlike during wakefulness, the recurrent excitation within the action neuron population is absent during NREM sleep.

Likely REM → wakefulness transition. During REM sleep, REM neurons excite arousal neurons, which in turn excite action neurons (**Figure 3*c***). To maintain REM sleep, the inhibition of action neurons by REM neurons must be stronger than the excitation from arousal neurons. Even a slight shift in this balance that causes a partial activation of action neurons can lead to a rise of their recurrent excitation, triggering a positive feedback cascade that quickly overcomes the inhibition by REM neurons. This could explain why in humans spontaneous awakening is most likely to occur following REM sleep, and rodents typically wake up after REM sleep rather than transitioning back into NREM sleep. In short, the high REM sleep to wakefulness transition probability is due to the existence of wake/REM sleep–active but wake-promoting arousal neurons highlighted in the AA model.

Neuronal Instantiation of the Arousal-Action Model

For each cell category depicted in the conceptual model (**Figure 3*b***), there are known neurons exhibiting matching properties.

Arousal neurons. Cholinergic, glutamatergic, and parvalbumin (PV)-expressing GABAergic neurons in the basal forebrain are wake/REM sleep active, but their optogenetic activation promotes only wakefulness (Xu et al. 2015). Although cholinergic neuron activation causes an immediate cortical desynchronization, it has no effect on the speed of locomotion (Pinto et al. 2013), fitting the description of arousal neurons (**Figure 2*a***). Cholinergic neurons in the PPT and LDT are also wake/REM sleep active (Boucetta et al. 2014, Datta & Siwek 2002), and their activation causes cortical desynchronization without driving locomotion (Caggiano et al. 2018, Roseberry et al. 2016). However, whether they are wakefulness or REM sleep promoting remains to be clarified (Kroeger et al. 2017, Van Dort et al. 2015). In addition, glutamatergic neurons in midline thalamic nuclei show high activity during wakefulness and REM sleep, and their activation/inactivation promotes/suppresses wakefulness (Gent et al. 2018, Glenn & Steriade 1982, Honjoh et al. 2018, Matyas et al. 2018, Ren et al. 2018).

Action neurons. Monoaminergic neurons in the ascending activating system are known to be wake active (Aston-Jones & Bloom 1981; Jacobs & Fornal 1991; Takahashi et al. 2006, 2010) and wake promoting (Carter et al. 2010, Cho et al. 2017, Eban-Rothschild et al. 2016, Lu et al. 2006a, Monti 2011, Yu et al. 2015). Some of them can also enhance the excitability of spinal motor neurons (Holstege & Kuypers 1987, White et al. 1991) and invigorate movement (da Silva et al. 2018), fitting the description of action neurons (**Figure 2*a***). Glutamatergic neurons in the mesencephalic locomotor region (which overlaps with the PPT) strongly promote wakefulness and locomotion (Caggiano et al. 2018, Kroeger et al. 2017, Lee et al. 2014, Roseberry et al. 2016); a subset of them are selectively wake active (Boucetta et al. 2014). Orexin/hypocretin neurons also fire selectively during wakefulness, especially during active exploration (Lee et al. 2005, Mileykovskiy et al. 2005). The recurrent excitation among them (Li et al. 2002, Yamanaka et al. 2010) and their excitatory projections to monoaminergic neurons (Inutsuka & Yamanaka 2013) are likely to play a crucial role in the stabilization of wakefulness (Adamantidis et al. 2007). In addition, glutamatergic neurons in the PB expressing calcitonin gene-related peptide (CGRP) signal pain and threat (Campos et al. 2018, Han et al. 2015), and their activation promotes wakefulness (Kaur et al. 2017). These neurons, located at a key position of the central autonomic network, represent strong candidates for action neurons.

NREM neurons. Activation of GABAergic neurons in the PZ (Anaclet et al. 2014) or SOM-expressing GABAergic neurons in the basal forebrain (Xu et al. 2015) promotes NREM sleep; a subset of the neurons in each population are NREM active (Alam et al. 2018) (**Figure 2*b***). GABAergic neurons in the vlPAG strongly promote NREM sleep by suppressing both wakefulness and REM sleep, although their firing rates are higher during wakefulness than NREM sleep (Weber et al. 2015, 2018). Galanin-expressing neurons in the DMH that project to the POA are both NREM active and NREM promoting (Chen et al. 2018). Several other populations have been shown to specifically promote NREM sleep, including the POA neurons activated by the $\alpha 2$ adrenergic receptor agonist dexmedetomidine (Zhang et al. 2015), TAC1- and PDYN-expressing GABAergic neurons in the lateral POA (Chung et al. 2017), warm-sensing neurons in the median/medial POA (Harding et al. 2018), a subset of glutamatergic neurons in the pontine tegmentum (Hayashi et al. 2015), and adenosine A2A receptor-expressing neurons in the dorsal and ventral striatum (Oishi et al. 2017, Yuan et al. 2017). However, whether these neurons are selectively active during NREM sleep remains to be investigated.

REM neurons. GABAergic neurons in the LPGi are REM active and strongly REM promoting (Weber et al. 2015) (**Figure 2*c***). In the DMH, the galanin-expressing neurons projecting to the

raphe pallidus are also REM active and REM promoting (Chen et al. 2018). In addition, REM sleep can be induced by activating the dorsal pontine tegmentum of cats and rats (Amatruda et al. 1975, Boissard et al. 2002, George et al. 1964, Gnadt & Pegram 1986) where a subset of glutamatergic neurons are REM active (Clement et al. 2011, Lu et al. 2006b). However, due to the close proximity between REM sleep– and wake-active neurons in the mouse (Cox et al. 2016), selective targeting of REM neurons remains challenging.

In addition to the neurons that specifically promote REM or NREM sleep, there are also populations that promote both types of sleep. These include CCK and CRH neurons in the POA (Chung et al. 2017), MCH neurons in the lateral hypothalamus (Jego et al. 2013, Konadhode et al. 2013, Tsunematsu et al. 2014), and GABAergic neurons in the ZI (Liu et al. 2017) and SNr (Liu et al. 2018) (**Figure 2*b***). However, it remains possible that within each population there are distinct subsets of neurons that promote REM versus NREM sleep.

Connections among neuronal categories. The functional interactions in the AA model (**Figure 3*b***) are consistent with many experimentally established synaptic connections between sleep and wake neurons. For example, action neurons are expected to be inhibited by both REM and NREM sleep neurons. Indeed, orexin/hypocretin neurons are innervated by MCH neurons in the lateral hypothalamus (Guan et al. 2002) and GABAergic neurons in the ZI (Liu et al. 2017). Histaminergic neurons in the TMN are inhibited by the POA neurons promoting both REM and NREM sleep (Chung et al. 2017), and LC noradrenergic, DR serotonergic, VTA dopaminergic, and PPT glutamatergic neurons all receive GABAergic inputs from the SNr (Liu et al. 2018). In addition, both the GABAergic REM sleep neurons in the LPGi (Weber et al. 2015) and NREM sleep neurons in the vlPAG (Weber et al. 2018) project to the LC (Aston-Jones et al. 1986, Sirieix et al. 2012) even though the two GABAergic populations play antagonistic roles in REM/NREM sleep alternation. Glutamatergic neurons in the PB, which strongly promote wakefulness (Fuller et al. 2011, Kaur et al. 2017), receive projections from NREM sleep–promoting PZ GABAergic neurons (Anaclet et al. 2012, 2014). Another prediction of the AA model is that arousal neurons should be inhibited by NREM sleep neurons. In the basal forebrain, cholinergic, glutamatergic, and PV-positive GABAergic neurons all receive local inhibition from SOM-expressing GABAergic neurons, which promote NREM sleep (Xu et al. 2015).

Model-Guided Identification of New Sleep Neurons

In addition to conceptualizing the known wakefulness and REM and NREM sleep neurons and their interactions, the AA model could also provide a blueprint for discovering new sleep neurons. As NREM sleep neurons are predicted to inhibit both arousal and action neurons (**Figure 3*b***), one can perform a whole-brain screening for candidate NREM sleep neurons using retrograde tracing from the known arousal and action populations. Of course, each population of wake-promoting neurons may receive inhibitory inputs from multiple sources, many of which may be unrelated to sleep. However, neurons that broadly inhibit multiple arousal or action populations are strong candidates for NREM sleep neurons. Similarly, inhibitory neurons that target action and NREM sleep neurons are good candidates for REM sleep neurons. In principle, excitatory neurons that innervate sleep neurons could also promote sleep. One can thus retrogradely trace from identified sleep neurons to identify their excitatory inputs. Once the candidate sleep neurons are identified anatomically, functional validation experiments should be performed to test whether they are sleep active and sleep promoting using a variety of techniques (Weber & Dan 2016).

It is worth noting that, unlike the somatomotor system (SMS), autonomic activation is controlled by the separate sympathetic nervous system (SNS) and parasympathetic nervous system

(PSNS). The distinct sympathetic/parasympathetic activity profiles across different brain states lead to specific predictions about circuit connectivity: NREM sleep neurons should suppress sympathetic and/or promote parasympathetic activity, although REM sleep neurons may exert complex influences on autonomic activity (Jones 2009). Thus, in addition to the connections with the well-known arousal and action neurons in the central nervous system, analyses of the interactions with the SMS, SNS, and PSNS (**Figure 3*d***) may provide an additional strategy for both the identification of new REM and NREM sleep neurons and verification/falsification of the AA model. Strong coupling between brain functions and motor states of the animal has been demonstrated in both flies and mammals (Lee et al. 2014, Maimon et al. 2010, McGinley et al. 2015, Niell & Stryker 2010, Polack et al. 2013, Poulet & Petersen 2008, Vinck et al. 2015). The fact that many sleep neurons are part of the somatic and autonomic motor circuits may help to ensure the coupling across all behavioral states. It also suggests that a primary function of sleep is to facilitate biological processes that require behavioral quiescence.

SUMMARY

Fueled by recent technical innovations that allow selective targeting of genetically defined cell types for both observation and manipulation of their activity, studies in the past few years have identified multiple REM and NREM sleep neuron populations. In contrast to the circadian rhythm, which is controlled by a central master clock in the suprachiasmatic nucleus (Hastings et al. 2018), the sleep control system may be organized by a different principle. We believe that a fundamental reason for the highly distributed sleep control network is the need to coordinate changes in autonomic and somatomotor activity with brain state switches. To generate the global state of sleep, the control mechanism infiltrates major nodes of the central autonomic and somatomotor networks, resulting in a broad distribution of neurons promoting REM and NREM sleep. The proposed AA model can incorporate a variety of experimentally characterized sleep- and wakefulness-promoting neurons and explain key features of transitions between wakefulness and REM and NREM sleep states. Network models based on limited sleep neuron populations were previously constructed to simulate brain state transitions (Behn et al. 2007, Phillips & Robinson 2007, Phillips et al. 2010, Rempe et al. 2010, Tamakawa et al. 2006). In future studies, it would be of great interest to implement the AA model with biophysically realistic wakefulness and REM and NREM sleep neurons to test its explanatory power.

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LITERATURE CITED

Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. 2007. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature* 450:420–24

Alam MA, Kostin A, Siegel J, McGinty D, Szymusiak R, Alam MN. 2018. Characteristics of sleep-active neurons in the medullary parafacial zone in rats. *Sleep* 41:zsy130

Amatruda TT 3rd, Black DA, McKenna TM, McCarley RW, Hobson JA. 1975. Sleep cycle control and cholinergic mechanisms: differential effects of carbachol injections at pontine brain stem sites. *Brain Res.* 98:501–15

Anaclet C, Ferrari L, Arrigoni E, Bass CE, Saper CB, et al. 2014. The GABAergic parafacial zone is a medullary slow wave sleep-promoting center. *Nat. Neurosci.* 17:1217–24

Anaclet C, Lin JS, Vetrivelan R, Krenzer M, Vong L, et al. 2012. Identification and characterization of a sleep-active cell group in the rostral medullary brainstem. *J. Neurosci.* 32:17970–76

Aserinsky E, Kleitman N. 1953. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 118:273–74

Aston-Jones G, Bloom FE. 1981. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J. Neurosci.* 1:876–86

Aston-Jones G, Ennis M, Pieribone VA, Nickell WT, Shipley MT. 1986. The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network. *Science* 234:734–37

Bandler R, Keay KA. 1996. Columnar organization in the midbrain periaqueductal gray and the integration of emotional expression. *Prog. Brain Res.* 107:285–300

Barlow IL, Rihel J. 2017. Zebrafish sleep: from geneZZZ to neuronZZZ. *Curr. Opin. Neurobiol.* 44:65–71

Batini C, Moruzzi G, Palestini M, Rossi GF, Zanchetti A. 1958. Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. *Science* 128:30–32

Beaulieu P, Lambert C. 1998. Peptidic regulation of heart rate and interactions with the autonomic nervous system. *Cardiovasc. Res.* 37:578–85

Behbehani MM. 1995. Functional characteristics of the midbrain periaqueductal gray. *Prog. Neurobiol.* 46:575–605

Behn CG, Brown EN, Scammell TE, Kopell NJ. 2007. Mathematical model of network dynamics governing mouse sleep-wake behavior. *J. Neurophysiol.* 97:3828–40

Boissard R, Gervasoni D, Schmidt MH, Barbagli B, Fort P, Luppi PH. 2002. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur. J. Neurosci.* 16:1959–73

Boucetta S, Cisse Y, Mainville L, Morales M, Jones BE. 2014. Discharge profiles across the sleep-waking cycle of identified cholinergic, GABAergic, and glutamatergic neurons in the pontomesencephalic tegmentum of the rat. *J. Neurosci.* 34:4708–27

Broughton R, Valley V, Aguirre M, Roberts J, Suwalski W, Dunham W. 1986. Excessive daytime sleepiness and the pathophysiology of narcolepsy-cataplexy: a laboratory perspective. *Sleep* 9:205–15

Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. 2012. Control of sleep and wakefulness. *Physiol. Rev.* 92:1087–187

Buzsaki G, Bickford RG, Ponomareff G, Thal LJ, Mandel R, Gage FH. 1988. Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *J. Neurosci.* 8:4007–26

Caggiano V, Leiras R, Goni-Erro H, Masini D, Bellardita C, et al. 2018. Midbrain circuits that set locomotor speed and gait selection. *Nature* 553:455–60

Campbell SS, Tobler I. 1984. Animal sleep: a review of sleep duration across phylogeny. *Neurosci. Biobehav. Rev.* 8:269–300

Campos CA, Bowen AJ, Roman CW, Palmiter RD. 2018. Encoding of danger by parabrachial CGRP neurons. *Nature* 555:617–22

Capelli P, Pivetta C, Esposito MS, Arber S. 2017. Locomotor speed control circuits in the caudal brainstem. *Nature* 551:373–77

Carrive P. 1993. The periaqueductal gray and defensive behavior: functional representation and neuronal organization. *Behav. Brain Res.* 58:27–47

Carter ME, Yizhar O, Chikahisa S, Nguyen H, Adamantidis A, et al. 2010. Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat. Neurosci.* 13:1526–33

Cetin A, Callaway EM. 2014. Optical control of retrogradely infected neurons using drug-regulated "TLoop" lentiviral vectors. *J. Neurophysiol.* 111:2150–59

Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, et al. 1999. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 98:437–51

Chen KS, Xu M, Zhang Z, Chang WC, Gaj T, et al. 2018. A hypothalamic switch for REM and non-REM sleep. *Neuron* 97:1168–76.e4

Cho JR, Treweek JB, Robinson JE, Xiao C, Bremner LR, et al. 2017. Dorsal raphe dopamine neurons modulate arousal and promote wakefulness by salient stimuli. *Neuron* 94:1205–19.e8

Chung S, Weber F, Zhong P, Tan CL, Nguyen TN, et al. 2017. Identification of preoptic sleep neurons using retrograde labelling and gene profiling. *Nature* 545:477–81

Clement O, Sapin E, Berod A, Fort P, Luppi PH. 2011. Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep* 34:419–23

Cox J, Pinto L, Dan Y. 2016. Calcium imaging of sleep-wake related neuronal activity in the dorsal pons. *Nat. Commun.* 7:10763

da Silva JA, Tecuapetla F, Paixao V, Costa RM. 2018. Dopamine neuron activity before action initiation gates and invigorates future movements. *Nature* 554:244–48

Datta S, Siwek DF. 2002. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep-wake cycle in the freely moving rats. *J. Neurosci. Res.* 70:611–21

de Zambotti M, Trinder J, Silvani A, Colrain IM, Baker FC. 2018. Dynamic coupling between the central and autonomic nervous systems during sleep: a review. *Neurosci. Biobehav. Rev.* 90:84–103

Deisseroth K. 2011. Optogenetics. *Nat. Methods* 8:26–29

Eban-Rothschild A, Rothschild G, Giardino WJ, Jones JR, de Lecea L. 2016. VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. *Nat. Neurosci.* 19:1356–66

Eguchi K, Satoh T. 1980. Characterization of the neurons in the region of solitary tract nucleus during sleep. *Physiol. Behav.* 24:99–102

Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. 2011. Reassessment of the structural basis of the ascending arousal system. *J. Comp. Neurol.* 519:933–56

Gent TC, Bandarabadi M, Herrera CG, Adamantidis AR. 2018. Thalamic dual control of sleep and wakefulness. *Nat. Neurosci.* 21:974–84

George R, Haslett WL, Jenden DJ. 1964. A cholinergic mechanism in the brainstem reticular formation: induction of paradoxical sleep. *Int. J. Neuropharmacol.* 3:541–52

Gerashchenko D, Blanco-Centurion CA, Miller JD, Shiromani PJ. 2006. Insomnia following hypocretin2-saporin lesions of the substantia nigra. *Neuroscience* 137:29–36

Gerfen CR, Surmeier DJ. 2011. Modulation of striatal projection systems by dopamine. *Annu. Rev. Neurosci.* 34:441–66

Glenn LL, Steriade M. 1982. Discharge rate and excitability of cortically projecting intralaminar thalamic neurons during waking and sleep states. *J. Neurosci.* 2:1387–404

Gnadt JW, Pegram GV. 1986. Cholinergic brainstem mechanisms of REM sleep in the rat. *Brain Res.* 384:29–41

Gong H, McGinty D, Guzman-Marin R, Chew KT, Stewart D, Szymusiak R. 2004. Activation of c-fos in GABAergic neurones in the preoptic area during sleep and in response to sleep deprivation. *J. Physiol.* 556:935–46

Guan JL, Uehara K, Lu S, Wang QP, Funahashi H, et al. 2002. Reciprocal synaptic relationships between orexin- and melanin-concentrating hormone-containing neurons in the rat lateral hypothalamus: a novel circuit implicated in feeding regulation. *Int. J. Obes. Relat. Metab. Disord.* 26:1523–32

Han S, Soleiman MT, Soden ME, Zweifel LS, Palmiter RD. 2015. Elucidating an affective pain circuit that creates a threat memory. *Cell* 162:363–74

Harding EC, Yu X, Miao A, Andrews N, Ma Y, et al. 2018. A neuronal hub binding sleep initiation and body cooling in response to a warm external stimulus. *Curr. Biol.* 28:2263–73.e4

Hassani OK, Lee MG, Henny P, Jones BE. 2009a. Discharge profiles of identified GABAergic in comparison to cholinergic and putative glutamatergic basal forebrain neurons across the sleep-wake cycle. *J. Neurosci.* 29:11828–40

Hassani OK, Lee MG, Jones BE. 2009b. Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. *PNAS* 106:2418–22

Hastings MH, Maywood ES, Brancaccio M. 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. *Nat. Rev. Neurosci.* 19:453–69

Hayashi Y, Kashiwagi M, Yasuda K, Ando R, Kanuka M, et al. 2015. Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice. *Science* 350:957–61

Hendricks JC, Finn SM, Panckeri KA, Chavkin J, Williams JA, et al. 2000. Rest in *Drosophila* is a sleep-like state. *Neuron* 25:129–38

Hobson JA, McCarley RW, Wyzinski PW. 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science* 189:55–58

Holstege JC, Kuypers HG. 1987. Brainstem projections to spinal motoneurons: an update. *Neuroscience* 23:809–21

Honjoh S, Sasai S, Schiereck SS, Nagai H, Tononi G, Cirelli C. 2018. Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. *Nat. Commun.* 9:2100

Inutsuka A, Yamanaka A. 2013. The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions. *Front. Endocrinol.* 4:18

Jacobs BL, Fornal CA. 1991. Activity of brain serotonergic neurons in the behaving animal. *Pharmacol. Rev.* 43:563–78

Jafari B. 2017. Sleep architecture and blood pressure. *Sleep Med. Clin.* 12:161–66

Jego S, Glasgow SD, Herrera CG, Ekstrand M, Reed SJ, et al. 2013. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. *Nat. Neurosci.* 16:1637–43

Jones B. 2009. Sleep-wake autonomic regulation. In *Encyclopedia of Neuroscience*, ed. MD Binder, N Hirokawa, U Windhorst, pp. 3732–36. Berlin: Springer-Verlag

Jouvet M. 1962. [Research on the neural structures and responsible mechanisms in different phases of physiological sleep]. *Arch. Ital. Biol.* 100:125–206 (In French)

Kaur S, Thankachan S, Begum S, Liu M, Blanco-Centurion C, Shiromani PJ. 2009. Hypocretin-2 saporin lesions of the ventrolateral periaquaductal gray (*vl*PAG) increase REM sleep in hypocretin knockout mice. *PLOS ONE* 4:e6346

Kaur S, Wang JL, Ferrari L, Thankachan S, Kroeger D, et al. 2017. A genetically defined circuit for arousal from sleep during hypercapnia. *Neuron* 96:1153–67.e5

Khalighi S, Sousa T, Santos JM, Nunes U. 2016. ISRUC-Sleep: a comprehensive public dataset for sleep researchers. *Comput. Methods Programs Biomed.* 124:180–92

Kohyama J, Lai YY, Siegel JM. 1998. Inactivation of the pons blocks medullary-induced muscle tone suppression in the decerebrate cat. *Sleep* 21:695–99

Konadhode RR, Pelluru D, Blanco-Centurion C, Zayachkivsky A, Liu M, et al. 2013. Optogenetic stimulation of MCH neurons increases sleep. *J. Neurosci.* 33:10257–63

Krauchi K, Cajochen C, Werth E, Wirz-Justice A. 1999. Warm feet promote the rapid onset of sleep. *Nature* 401:36–37

Kravitz AV, Freeze BS, Parker PR, Kay K, Thwin MT, et al. 2010. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. *Nature* 466:622–26

Krenzer M, Anaclet C, Vetrivelan R, Wang N, Vong L, et al. 2011. Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PLOS ONE* 6:e24998

Kroeger D, Ferrari LL, Petit G, Mahoney CE, Fuller PM, et al. 2017. Cholinergic, glutamatergic, and GABAergic neurons of the pedunculopontine tegmental nucleus have distinct effects on sleep/wake behavior in mice. *J. Neurosci.* 37:1352–66

Lai YY, Shalita T, Hajnik T, Wu JP, Kuo JS, et al. 1999. Neurotoxic *N*-methyl-D-aspartate lesion of the ventral midbrain and mesopontine junction alters sleep-wake organization. *Neuroscience* 90:469–83

Lee AM, Hoy JL, Bonci A, Wilbrecht L, Stryker MP, Niell CM. 2014. Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. *Neuron* 83:455–66

Lee MG, Hassani OK, Jones BE. 2005. Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. *J. Neurosci.* 25:6716–20

Li Y, Gao XB, Sakurai T, van den Pol AN. 2002. Hypocretin/orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system. *Neuron* 36:1169–81

Lin JS, Sakai K, Vanni-Mercier G, Jouvet M. 1989. A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. *Brain Res.* 479:225–40

Lin L, Faraco J, Li R, Kadotani H, Rogers W, et al. 1999. The sleep disorder canine narcolepsy is caused by a mutation in the *hypocretin (orexin) receptor 2* gene. *Cell* 98:365–76

Liu D, Ma C, Zheng W, Yao Y, Dan Y. 2018. Sleep and motor control by a basal ganglia circuit. bioRxiv 405324. **https://doi.org/10.1101/405324**

Liu K, Kim J, Kim DW, Zhang YS, Bao H, et al. 2017. Lhx6-positive GABA-releasing neurons of the zona incerta promote sleep. *Nature* 548:582–87

Llewellyn-Smith IJ, Verberne AJM, eds. 2011. *Central Regulation of Autonomic Functions*. New York: Oxford Univ. Press. 2nd ed.

Lu J, Greco MA, Shiromani P, Saper CB. 2000. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J. Neurosci.* 20:3830–42

Lu J, Jhou TC, Saper CB. 2006a. Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. *J. Neurosci.* 26:193–202

Lu J, Sherman D, Devor M, Saper CB. 2006b. A putative flip-flop switch for control of REM sleep. *Nature* 441:589–94

Magnes J, Moruzzi G, Pompeiano O, US Air Force. 1960. *Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract*. Rep., US Air Force Off. Sci. Res., Air Res. Dev. Command, Washington, DC

Magoun HW, Rhines R. 1946. An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.* 9:165–71

Maimon G, Straw AD, Dickinson MH. 2010. Active flight increases the gain of visual motion processing in *Drosophila*. *Nat. Neurosci*. 13:393–99

Maloney KJ, Mainville L, Jones BE. 2000. c-Fos expression in GABAergic, serotonergic, and other neurons of the pontomedullary reticular formation and raphe after paradoxical sleep deprivation and recovery. *J. Neurosci.* 20:4669–79

Matyas F, Komlosi G, Babiczky A, Kocsis K, Bartho P, et al. 2018. A highly collateralized thalamic cell type with arousal-predicting activity serves as a key hub for graded state transitions in the forebrain. *Nat. Neurosci.* 21:1551–62

McCarley RW, Hobson JA. 1975. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science* 189:58–60

McGinley MJ, David SV, McCormick DA. 2015. Cortical membrane potential signature of optimal states for sensory signal detection. *Neuron* 87:179–92

McGinty DJ, Sterman MB. 1968. Sleep suppression after basal forebrain lesions in the cat. *Science* 160:1253–55

Mileykovskiy BY, Kiyashchenko LI, Siegel JM. 2005. Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron* 46:787–98

Modirrousta M, Mainville L, Jones BE. 2004. Gabaergic neurons with $\alpha 2$-adrenergic receptors in basal forebrain and preoptic area express c-Fos during sleep. *Neuroscience* 129:803–10

Monti JM. 2011. Serotonin control of sleep-wake behavior. *Sleep Med. Rev.* 15:269–81

Morairty SR, Szymusiak R, Thomson D, McGinty DJ. 1993. Selective increases in non-rapid eye movement sleep following whole body heating in rats. *Brain Res.* 617:10–16

Moruzzi G, Magoun HW. 1949. Brain stem reticular formation and activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.* 1:455–73

Nath RD, Bedbrook CN, Abrams MJ, Basinger T, Bois JS, et al. 2017. The jellyfish *Cassiopea* exhibits a sleep-like state. *Curr. Biol.* 27:2984–90.e3

Nauta WJ. 1946. Hypothalamic regulation of sleep in rats; an experimental study. *J. Neurophysiol.* 9:285–316

Niell CM, Stryker MP. 2010. Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65:472–79

Oh SW, Harris JA, Ng L, Winslow B, Cain N, et al. 2014. A mesoscale connectome of the mouse brain. *Nature* 508:207–14

Oishi Y, Xu Q, Wang L, Zhang BJ, Takahashi K, et al. 2017. Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice. *Nat. Commun.* 8:734

Osakada F, Callaway EM. 2013. Design and generation of recombinant rabies virus vectors. *Nat. Protoc.* 8:1583–601

Phillips AJ, Robinson PA. 2007. A quantitative model of sleep-wake dynamics based on the physiology of the brainstem ascending arousal system. *J. Biol. Rhythms* 22:167–79

Phillips AJ, Robinson PA, Kedziora DJ, Abeysuriya RG. 2010. Mammalian sleep dynamics: how diverse features arise from a common physiological framework. *PLOS Comput. Biol.* 6:e1000826

Pinto L, Goard MJ, Estandian D, Xu M, Kwan AC, et al. 2013. Fast modulation of visual perception by basal forebrain cholinergic neurons. *Nat. Neurosci.* 16:1857–63

Polack PO, Friedman J, Golshani P. 2013. Cellular mechanisms of brain state–dependent gain modulation in visual cortex. *Nat. Neurosci.* 16:1331–39

Poulet JF, Petersen CC. 2008. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature* 454:881–85

Qiu MH, Vetrivelan R, Fuller PM, Lu J. 2010. Basal ganglia control of sleep-wake behavior and cortical activation. *Eur. J. Neurosci.* 31:499–507

Raizen DM, Zimmerman JE, Maycock MH, Ta UD, You YJ, et al. 2008. Lethargus is a *Caenorhabditis elegans* sleep-like state. *Nature* 451:569–72

Rempe MJ, Best J, Terman D. 2010. A mathematical model of the sleep/wake cycle. *J. Math. Biol.* 60:615–44

Ren SC, Wang YL, Yue FG, Cheng XF, Dang RZ, et al. 2018. The paraventricular thalamus is a critical thalamic area for wakefulness. *Science* 362:429–34

Roseberry TK, Lee AM, Lalive AL, Wilbrecht L, Bonci A, Kreitzer AC. 2016. Cell-type-specific control of brainstem locomotor circuits by basal ganglia. *Cell* 164:526–37

Sallanon M, Denoyer M, Kitahama K, Aubert C, Gay N, Jouvet M. 1989. Long-lasting insomnia induced by preoptic neuron lesions and its transient reversal by muscimol injection into the posterior hypothalamus in the cat. *Neuroscience* 32:669–83

Saper CB, Chou TC, Scammell TE. 2001. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci.* 24:726–31

Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. 2010. Sleep state switching. *Neuron* 68:1023–42

Sapin E, Lapray D, Berod A, Goutagny R, Leger L, et al. 2009. Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. *PLOS ONE* 4:e4272

Sastre JP, Buda C, Kitahama K, Jouvet M. 1996. Importance of the ventrolateral region of the periaqueductal gray and adjacent tegmentum in the control of paradoxical sleep as studied by muscimol microinjections in the cat. *Neuroscience* 74:415–26

Scammell TE, Arrigoni E, Lipton JO. 2017. Neural circuitry of wakefulness and sleep. *Neuron* 93:747–65

Schenkel E, Siegel JM. 1989. REM sleep without atonia after lesions of the medial medulla. *Neurosci. Lett.* 98:159–65

Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. 2000. Correlates of sleep and waking in *Drosophila melanogaster*. *Science* 287:1834–37

Shein-Idelson M, Ondracek JM, Liaw HP, Reiter S, Laurent G. 2016. Slow waves, sharp waves, ripples, and REM in sleeping dragons. *Science* 352:590–95

Sherin JE, Elmquist JK, Torrealba F, Saper CB. 1998. Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. *J. Neurosci.* 18:4705–21

Sherin JE, Shiromani PJ, McCarley RW, Saper CB. 1996. Activation of ventrolateral preoptic neurons during sleep. *Science* 271:216–19

Silvani A, Dampney RA. 2013. Central control of cardiovascular function during sleep. *Am. J. Physiol. Heart Circ. Physiol.* 305:H1683–92

Sirieix C, Gervasoni D, Luppi PH, Leger L. 2012. Role of the lateral paragigantocellular nucleus in the network of paradoxical (REM) sleep: an electrophysiological and anatomical study in the rat. *PLOS ONE* 7:e28724

Steininger TL, Gong H, McGinty D, Szymusiak R. 2001. Subregional organization of preoptic area/anterior hypothalamic projections to arousal-related monoaminergic cell groups. *J. Comp. Neurol.* 429:638–53

Sternson SM, Roth BL. 2014. Chemogenetic tools to interrogate brain functions. *Annu. Rev. Neurosci.* 37:387–407

Szymusiak R, Alam N, Steininger TL, McGinty D. 1998. Sleep-waking discharge patterns of ventrolateral preoptic/anterior hypothalamic neurons in rats. *Brain Res.* 803:178–88

Szymusiak R, McGinty D. 1989. Sleep-waking discharge of basal forebrain projection neurons in cats. *Brain Res. Bull.* 22:423–30

Takahashi K, Kayama Y, Lin JS, Sakai K. 2010. Locus coeruleus neuronal activity during the sleep-waking cycle in mice. *Neuroscience* 169:1115–26

Takahashi K, Lin JS, Sakai K. 2006. Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. *J. Neurosci.* 26:10292–98

Takahashi K, Lin JS, Sakai K. 2009. Characterization and mapping of sleep-waking specific neurons in the basal forebrain and preoptic hypothalamus in mice. *Neuroscience* 161:269–92

Tamakawa Y, Karashima A, Koyama Y, Katayama N, Nakao M. 2006. A quartet neural system model orchestrating sleep and wakefulness mechanisms. *J. Neurophysiol.* 95:2055–69

Tian L, Hires SA, Looger LL. 2012. Imaging neuronal activity with genetically encoded calcium indicators. *Cold Spring Harb. Protoc.* 2012:647–56

Tovote P, Esposito MS, Botta P, Chaudun F, Fadok JP, et al. 2016. Midbrain circuits for defensive behaviour. *Nature* 534:206–12

Tsunematsu T, Ueno T, Tabuchi S, Inutsuka A, Tanaka KF, et al. 2014. Optogenetic manipulation of activity and temporally controlled cell-specific ablation reveal a role for MCH neurons in sleep/wake regulation. *J. Neurosci.* 34:6896–909

Van Dort CJ, Zachs DP, Kenny JD, Zheng S, Goldblum RR, et al. 2015. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. *PNAS* 112:584–89

Van Someren EJ. 2006. Mechanisms and functions of coupling between sleep and temperature rhythms. *Prog. Brain Res.* 153:309–24

Vanini G, Torterolo P, McGregor R, Chase MH, Morales FR. 2007. GABAergic processes in the mesencephalic tegmentum modulate the occurrence of active (rapid eye movement) sleep in guinea pigs. *Neuroscience* 145:1157–67

Vinck M, Batista-Brito R, Knoblich U, Cardin JA. 2015. Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. *Neuron* 86:740–54

Von Economo C. 1930. Sleep as a problem of localization. *J. Nerv. Ment. Dis.* 71:249–59

Weber F, Chung S, Beier KT, Xu M, Luo L, Dan Y. 2015. Control of REM sleep by ventral medulla GABAergic neurons. *Nature* 526:435–38

Weber F, Dan Y. 2016. Circuit-based interrogation of sleep control. *Nature* 538:51–59

Weber F, Hoang Do JP, Chung S, Beier KT, Bikov M, et al. 2018. Regulation of REM and non-REM sleep by periaqueductal GABAergic neurons. *Nat. Commun.* 9:354

Weissbourd B, Ren J, DeLoach KE, Guenthner CJ, Miyamichi K, Luo L. 2014. Presynaptic partners of dorsal raphe serotonergic and GABAergic neurons. *Neuron* 83:645–62

White SR, Fung SJ, Barnes CD. 1991. Norepinephrine effects on spinal motoneurons. *Prog. Brain Res.* 88:343–50

Xu M, Chung S, Zhang S, Zhong P, Ma C, et al. 2015. Basal forebrain circuit for sleep-wake control. *Nat. Neurosci.* 18:1641–47

Yamanaka A, Tabuchi S, Tsunematsu T, Fukazawa Y, Tominaga M. 2010. Orexin directly excites orexin neurons through orexin 2 receptor. *J. Neurosci.* 30:12642–52

Yang SR, Hu ZZ, Luo YJ, Zhao YN, Sun HX, et al. 2018. The rostromedial tegmental nucleus is essential for non-rapid eye movement sleep. *PLOS Biol.* 16:e2002909

Yu X, Ye Z, Houston CM, Zecharia AY, Ma Y, et al. 2015. Wakefulness is governed by GABA and histamine cotransmission. *Neuron* 87:164–78

Yuan XS, Wang L, Dong H, Qu WM, Yang SR, et al. 2017. Striatal adenosine A_{2A} receptor neurons control active-period sleep via parvalbumin neurons in external globus pallidus. *eLife* 6:e29055

Zhang Z, Ferretti V, Guntan I, Moro A, Steinberg EA, et al. 2015. Neuronal ensembles sufficient for recovery sleep and the sedative actions of α_2 adrenergic agonists. *Nat. Neurosci.* 18:553–61